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TRANSMITTAL FORM

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Total Number of Pages in This Submission

Application Number	09/994,909
Filing Date	11/23/2001
First Named Inventor	George Jackowski
Art Unit	1649
Examiner Name	Olga N. Chernyshev
Attorney Docket Number	2132.090

ENCLOSURES (*Check all that apply*)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
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- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

Applicant's Brief in accordance with 37 CFR 41.37 w/Appendix
A copy of the Non-Compliance Notice dtd 12/14/06

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	McHale & Slavin, P.A.		
Signature	Ferris H. Lander		
Printed name	Ferris H. Lander		
Date	1/16/2007	Reg. No.	43,377

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT	: Jackowski et al.
INVENTION	: **Complement C3 Precursor Biopolymer Markers Indicative of Alzheimer's Disease**
SERIAL NUMBER	: 09/994,909
FILING DATE	: November 23, 2001
EXAMINER	: Chernyshev, Olga N.
GROUP ART UNIT	: 1649
OUR FILE NO.	: 2132.090

Mail Stop Appeal Brief-Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

APPLICANT'S BRIEF IN ACCORDANCE WITH 37 C.F.R. § 41.37

Applicants submit this Appeal Brief to the Board of Patent Appeals and Interferences on appeal from the decision of Examiner Olga N. Chernyshev of Group Art Unit 1649 dated February 28, 2006, finally rejecting claim 1.

Express Mail No. EV842339817US

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Nanogen, Inc., the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

A similar appeal has also been filed by Appellants in US Application Serial Number 09/991,796 (attorney docket number 2132.109), filed on November 23, 2001, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. STATUS OF CLAIMS

Claims 1 and 39-46 are pending in the application. Claims 1-38 were originally presented. Claims 2-38 were cancelled without prejudice and new claims 39-46 were added by the amendment of November 3, 2003. Claims 39-46 were withdrawn from consideration on the merits based upon a restriction requirement. The final rejection of claim 1 under both 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is appealed. Claim 1 is shown in the attached Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Rejection mailed on February 28, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to a biopolymer marker, identified by the evaluation of a sample containing a plurality of biopolymers, which evidences a link to a specific disease state. See, specification at page 35, lines 14-18. Specifically, the biopolymer marker consists of amino acid residues 2-14 of SEQ ID NO:1 and evidences a link to Alzheimer's disease. Id. at page 46, lines 10-19 and Figures 1 and 2.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether Claim 1 is Unpatentable under 35 U.S.C. § 101 as Having No Specific and Substantial Credible Utility

1. Whether the Examiner Made a *Prima Facie* Showing that the Invention Lacks a Specific and Substantial Utility

2. Whether the Examiner Properly Held that Applicants' Asserted Utility Lacks Credibility

B. Whether Claim 1 is Unpatentable under 35 U.S.C. § 112, First Paragraph as Being Based on a Nonenabling Disclosure

1. Whether the Examiner Properly Evaluated the Application for Enablement.

VII. ARGUMENT

A. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 101

1. The Examiner Has Failed to Make a Prima Facie Showing that the Invention Lacks A Specific And Substantial Utility.

Claim 1, as shown in the attached Claims Appendix, stands finally rejected under 35 U.S.C. § 101. The Examiner maintains that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility.

Applicants respectfully traverse the rejection on the grounds that the application discloses an invention having specific, substantial, well-established and credible utility by showing an invention that is useful to the public as disclosed in its current form, rather than at some future date after further research, as a peptide marker linked to Alzheimer's disease. Furthermore, Applicants have supported this utility with data specifically directed to patients having Alzheimer's disease.

The standard for satisfying the requirements for utility under 35 U.S.C. § 101 is not particularly high. In most cases, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy 35 U.S.C. § 101. *See* In re Langer, 503 F.2d 1380, 1391, 183 USPQ 297 (CCPA 1974); MPEP § 2107.02(III)(A). In other words, the Office is correct to presume that a statement of utility made by an applicant is true.

Accordingly, the Examiner should presume that the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1) is useful as a marker for Alzheimer's disease based upon Applicants' showing in Figure 1 that the peptide is linked to Alzheimer's disease by its

differential expression in Alzheimer's disease patients as compared to age-matched control patients.

A "specific utility" refers to a utility that is well-defined, particular and specific to the subject matter claimed. Vague expressions such as "a compound has useful biological activity" or "biological properties" are meaningless. In re Fisher, 421 F.3d 1365, 1371, 76 USPQ2d 1225 (Fed. Cir. 2005); In re Kirk, 376 F.2d 936, 941, 153 USPQ 48 (CCPA 1967); MPEP § 2107.01. For example, a general statement indicating that a marker is useful for diagnostics, such as diagnosing a disease, would be insufficient, absent a disclosure of what disease and/or condition could be diagnosed. In contrast, a statement of diagnostic utility, such as diagnosing Alzheimer's disease, would be sufficient to identify a specific utility for the invention. Thus, Applicants' statement of utility regarding the use of the claimed peptide as a marker for Alzheimer's disease constitutes a specific utility since the claimed peptide is linked to the specific condition of Alzheimer's disease.

It is well known that pathological changes in an organism are reflected by changes observed in the serum protein pattern. For example, proteins that undergo a change in expression (from the normal) are often indicative of disease. A diagnosis may be predicted based upon the similarity of an unknown sample pattern to a known pattern of disease. Mass spectrometry is a tool used to establish serum protein patterns.

Generally proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are often first subjected to separation by polyacrylamide gel electrophoresis. Upon electrophoresis, the proteins contained in the sample separate into bands in specific areas of the gel according to weight and charge.

The separated protein bands which are observed and deemed to be different between two comparable states (for example, disease state vs. normal state) are excised from the gel and subjected to further fragmentation by enzymes. The resulting peptides are then collected and purified by chromatography prior to identification by mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The mass spectral profiles generated are composed of parts of the original protein and can be used to identify this protein.

In order for a rejection under 35 U.S.C. § 101 to be appropriate, the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention. In re Cortright, 165 F.3d 1353, 1355, 49 USPQ2d 1464 (Fed. Cir. 1999).

It is respectfully submitted that the "link to Alzheimer's disease" asserted by Applicants was elucidated under real-world conditions according to the methodology set forth in the following steps:

I. isolating peptides from body fluid samples obtained from two groups of patients; a) one group known to suffer from Alzheimer's disease; and b) a group of age-matched controls (healthy in regard to Alzheimer's disease);

II. carrying out the protocols disclosed in the specification on pages 37-47;

III. comparing the expression pattern of protein bands from the two groups of patients as evidenced in gels, such as that shown in Figure 1;

IV. subjecting the noted expression pattern to the criteria as disclosed in the specification at page 11, lines 9-20;

V. selecting and excising bands that are differentially expressed between the two groups, and, submitting the peptides present within the excised bands for further fragmentation and purification followed by sequence identification by mass spectrometry.

The Applicants, using the above-described methodology in a real-world environment, thereby elucidated and identified amino acid residues 2-14 of SEQ ID NO: 1 as a fragment of complement component 3 precursor protein found in healthy, control patients but found to be down-regulated in patients having Alzheimer's disease, thus establishing the instantly claimed link to Alzheimer's disease evidenced by the observed differential expression.

The characteristic mass spectral profile indicative of the claimed peptide is disclosed in Figure 2. Mass spectral profiles are reproducible and are typically published to provide established expression patterns for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profile (shown in Figure 2) provided in the instant specification as a reference for comparing with mass spectral profiles of peptides obtained from an unknown sample to test the unknown sample for a link to Alzheimer's disease through comparison of expression patterns, thereby demonstrating that the specification discloses a specific and substantial utility for the claimed peptide. This mass spectral profile is a showing of factual evidence that the claimed peptide could be used as a marker for Alzheimer's disease. Thus, the instant specification provides data (gel shown in Figure 1 and the mass spectral profile shown in Figure 2) supporting the desired results of the claimed invention; i.e. a biopolymer marker for Alzheimer's disease.

Accordingly, Applicants respectfully submit that the Examiner has failed to adhere to the precedent set in Cortright by failing to establish that there is a complete absence of data supporting the statements which sets forth the desired results of the claimed invention.

The Examiner notes that in the instant case, the specification discloses the finding of differential expression of protein 2-14 of SEQ ID NO: 1 in samples of patients with AD vs. normal patients and presents an assertion that this protein 2-14 of SEQ ID NO: 1 is useful as a marker of Alzheimer's disease. The Examiner asserts that it is obvious that a skilled practitioner would have to engage in significant further research to establish what amount of the instant claimed protein is diagnostic of Alzheimer's disease. However, with regard to providing a link to Alzheimer's disease as is instantly claimed, it is well settled that an applicant is not required to provide evidence of an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980); MPEP § 2107.02.

Thus, Applicants respectfully submit that providing an amount of the claimed marker that is diagnostic for Alzheimer's disease is not necessary to establish credibility of the asserted use for the claimed peptide as a marker for Alzheimer's disease. Accordingly, Applicants respectfully submit that the Examiner's requirement for such information is improper.

A "substantial utility" is a utility that defines a "real-world" use. MPEP § 2107.01(I). "Substantial utility" refers to a significant and presently-available benefit to the public. An application must show an invention that is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research.

"In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." Fisher, 421 F.3d at 1368, *citing* Nelson , 626 F.2d at 856.

In the context of an evaluation of substantial utility, the phrase "immediate benefit to the public" must not be interpreted to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Brenner v. Manson, 383 U.S. 519, 534-535, 148 USPQ 689 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". MPEP § 2107.01(I).

Additionally, care must be given not to find a lack of specific and substantial utility based upon the setting in which the invention is to be used. This is particularly important in biotechnology; for example, during examination of inventions to be used in a research or a laboratory setting. As the Federal Circuit noted:

> "An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact 'useful' in a patent sense. [The PTO] must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm." Fisher, 421 F.3d at 1372, *citing* MPEP § 2107.01(I).

Many research tools such as gas chromatographs, screening assays and nucleotide sequencing techniques have a clear, specific and unquestionable utility, e.g., they are useful in analyzing compounds). MPEP § 2107.01(I).

Furthermore, it has been established that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention

becomes useful is well before it is ready to be administered to humans. If Phase II testing was required in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *See* In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436 (Fed. Cir. 1995); MPEP § 2107.01(III).

The identification of the claimed peptide showing decreased expression in Alzheimer's disease relative to expression in an age-matched control population puts a researcher one step closer to understanding the pathogenesis of Alzheimer's disease and thus, also one step closer to improved diagnosis and treatment of Alzheimer's disease. The claimed peptide can be used immediately to screen patient populations for links to Alzheimer's disease or it can be used in further research to improve diagnosis and treatment of Alzheimer's disease. There is no question that improved diagnosis and treatment of Alzheimer's disease provides a tangible benefit to society; especially for the elderly population susceptible to the development of Alzheimer's disease. Since the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1) has a "real-world" use in its currently available form as a marker for Alzheimer's disease, the claimed peptide thus has a substantial utility.

Accordingly, there is a critical distinction between an invention that can be used in further experimentation and research, and an invention that requires further experimentation and research before it can be used. Applicants respectfully submit that the Examiner has erroneously found the claimed invention to be the latter rather than the former.

The Examiner cites Fisher in rejecting claim 1 and attempts to draw a parallel to the instant application by asserting that, just as in Fisher - where the Board reasoned that the use of the claimed expressed sequence tags ("ESTs") for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," Fisher, 421 F.3d at 1368 - the detection of peptide 2-14 of SEQ ID NO: 1 in a sample of a patient suspected of having Alzheimer's disease provides no meaningful information as to the diagnosis determination.

Applicants respectfully submit that the facts in Fisher are inapposite to those concerning the present application. Fisher's invention related to five purified nucleic acid sequences – ESTs - obtained from the leaf tissue of maize plants. As described in Fisher, an EST is a short nucleotide sequence that represents a fragment of a cDNA clone. It is typically generated by isolating a cDNA clone and sequencing a small number of nucleotides located at one end of the two cDNA strands. When an EST is introduced into a sample containing a mixture of DNA, the EST may hybridize with a portion of the DNA. Such binding shows that the gene corresponding to the EST was being expressed at the time of mRNA extraction.

Fisher disclosed in his application that the claimed ESTs may have been used in a variety of ways, including, for example, measuring the level of mRNA in a tissue sample via microarray technology to provide information about gene expression, isolating promoters and identifying the presence or absence of a polymorphism. Fisher, 421 F.3d at 1368. However, Fisher made no disclosure regarding the precise structure or function of

either the genes or the proteins encoded for by those genes to which the claimed ESTs correspond. Id.

The Examiner of the Fisher application rejected the claims for lack of utility under 35 U.S.C. § 101 and lack of enablement under 35 U.S.C. § 112, first paragraph. The Board affirmed the rejections. In upholding the rejection, the Court cited the guidelines in MPEP § 2107.01(I) that state a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. The Court noted the Applicants' admission that the underlying genes had no known functions, and that "[e]ssentially, the claimed ESTs act as no more than research intermediaries that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes". Id., at 1373. Accordingly, the Court found the ESTs to be mere "objects of use-testing", upon which scientific research could be performed with no assurance that anything useful will be discovered in the end. Id., *citing* Brenner, 383 U.S. at 535. Fisher's asserted uses represented merely hypothetical possibilities, objectives which the claimed ESTs, or any other EST for that matter, could possibly achieve, but none for which they have been used in the real world. For example, Fisher asserted that the ESTs could be used to identify polymorphisms or to isolate promoters. Nevertheless, in the face of a utility rejection, Fisher did not present any evidence showing that the ESTs had been used in either way. Id. Since nothing was known about the genes or proteins corresponding to the claimed ESTs, nothing set the claimed ESTs apart from the more than 32,000 ESTs disclosed in the application or from any EST derived from any organism. Id., at 1374. In other words, any EST could be

used to isolate any promoter. Furthermore, the use of the ESTs to actually identify the associated gene would constitute significant further experimentation, rendering the ESTs unable to be used in their current form. Ultimately, Fisher's ESTs were deemed only to be research intermediaries in the identification of underlying protein-encoding genes of unknown function. Id., at 1373.

In contrast to the invention of Fisher, the peptide of the instant invention is known to be a fragment of complement component 3 precursor protein having the amino acid sequence (i.e. structure) VYAYYNLEESCTR. Furthermore, the claimed peptide is disclosed as a marker of a specific disease condition, Alzheimer's disease. Any skilled artisan, without significant further research, could utilize the mass spectral profile of the claimed peptide, shown in Figure 2, as a reference for comparison with mass spectral profiles obtained from an unknown sample to screen the sample for a link to Alzheimer's disease through comparison of expression patterns.

Thus, Applicants respectfully submit that the Examiner's attempt to draw a parallel between Fisher and the instant application fails to support her finding a lack of specific and substantial utility, as the facts in Fisher are not akin to the instant application.

It is clear, from consideration of all of the foregoing remarks, that the claimed invention has a specific and substantial utility. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing for lack of specific and substantial utility.

2. The Examiner Improperly Finds Applicants' Asserted Utility Lacking in Credibility

The Examiner does not doubt or dispute the results of differential expression of the instant claimed protein 2-14 of SEQ ID NO:1. The main point of disagreement appears to be the interpretation of these results and what constitutes a specific, substantial and credible utility. Thus, the Examiner appears to believe that the showing of differential expression of the claimed peptide in Alzheimer's disease as compared to expression in age-matched controls is not sufficient to indicate that the claimed peptide could be used as a marker for Alzheimer's disease.

Applicants note that it is improper for Office personnel to merely question operability. Factual reasons must be set forth which would lead one of skill in the art to question the objective truth of the statement of operability. MPEP § 2107.02(IV).

The Examiner provides her opinion on what one of skill in the art would know. For example, the Examiner states that one skilled in the art readily appreciates that detection of differentially expressed proteins represents only the first step in identification of molecules that have a diagnostic potential and that one skilled in the art readily appreciates that many factors have a link to or are associated with a particular pathological condition. However, the Examiner does not provide reasoning or references evidencing why one of skill in the art would "readily appreciate" these things.

Furthermore, the Examiner requires Applicant to provide complete characterization of the claimed peptide, including data indicating what amount of the claimed peptide is diagnostic of Alzheimer's disease, to establish a utility for the claimed peptide.

The instant situation is akin to that in Cortright. Cortright's invention was drawn to a method for treating baldness by applying Bag Balm (a commercially available product used to soften cow udders) to human scalp. The Examiner of the Cortright application rejected the claim drawn to this invention under 35 U.S.C. § 101 as lacking utility. According to the Examiner, Cortright's statement of utility, i.e. her claims of treating baldness, were not credible because baldness was generally accepted in the art as being incurable. The Examiner therefore required clinical evidence to establish the claimed utility, which Cortright did not supply. Cortright, 165 F.3d at 1355.

The Board reversed the rejection under 35 U.S.C. § 101 because the Examiner did not set out sufficient reasons for finding Cortright's statements of utility incredible. The Board additionally noted that there is no per se requirement for clinical evidence to establish the utility of any invention. Id.

Applicants respectfully submit that the Examiner has similarly erred by improperly questioning the operability of the invention, in that she states what one of skill in the art would believe without providing evidence to support her conclusion. Additionally, Applicants respectfully submit that the Examiner has further erred by requiring Applicants to provide "complete characterization" of the claimed peptide in order to establish utility since precedent dictates that evidence of absolute certainty is not required.

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 US 835 (1984); MPEP § 2107.02(III)(A). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than

not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. MPEP § 2107.02(III)(A). Alternatively, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2164.07(I)(C).

Furthermore, an Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill in the art would not believe the applicants' assertion of utility. Brana, 51 F.3d at 1568; MPEP § 2107.01(III).

The prior art recognizes that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient (healthy with regard to Alzheimer's disease), it is immediately recognized as diagnostically valuable, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. This practice has been known in the art since at least 1992. *See* the abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992, copy attached hereto in the Evidence Appendix) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic marker for Alzheimer's disease. Since these practices are common, it is reasonable to believe that when one of skill in the art observes the differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased age-matched control patients; one of skill in the art would, more likely than not, connect this peptide with potential diagnostics and/or therapeutics for Alzheimer's disease.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1), a fragment of complement component 3 precursor, and Alzheimer's disease to be reasonable because there is a known association between Alzheimer's disease and the complement system. Multiple studies indicate that a chronic inflammatory state mediated by activation of the complement system exists in the Alzheimer's disease brain. *See* US 5,532,219, column 4, lines 25-40; Cooper et al. Immunology Research 21(2-3):159-165 2000; Emmerling et al. Biochim Biophys Acta 1502(1):158-171 2000; copies attached hereto in the Evidence Appendix.

The claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1), elucidated from and differentially expressed in diseased versus normal samples, is identified as a fragment of complement component 3 precursor protein at page 46, lines 10-19 of the specification as originally filed and is consistently replicated in the sample population. The gel shown in Figure 1 demonstrates that this peptide is down-regulated in Alzheimer's disease. This data is consistent with the studies indicating activation of complement in the pathology of Alzheimer's disease. Thus, Applicants hypothesized that complement is processed during the pathogenesis of Alzheimer's disease. One of skill in the art, considering the known inflammatory mechanisms involved in the development and progression of Alzheimer's disease, would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize the linkage between the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1); inflammation and Alzheimer's disease and thus would also find the suggestion of this peptide as a marker for Alzheimer's disease to be entirely reasonable.

One of ordinary skill in the art would conclude, based upon all of the foregoing remarks, that the asserted utility for the claimed peptide, use as a marker for Alzheimer's disease, is more likely than not true. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case for lack of credible utility.

B. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 112, First Paragraph.

1. The Examiner Improperly Finds the Invention Nonenabled

Claim 1, as shown in the attached Claims Appendix, stands finally rejected under 35 USC § 112, first paragraph.

It is well established that the enablement requirement of 35 U.S.C. § 112 incorporates the utility requirement of 35 U.S.C. § 101. Fisher, 421 F.3d at 1378. Where a written description fails to illuminate a credible utility, the PTO will make both a Section 112 rejection for failure to teach how to use the invention and a Section 101 rejection for lack of utility. Cortright, 165 F.3d at 1355. "If [certain] compositions are in fact useless, [a] specification cannot have taught how to use them." Id..

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the Court of Customs and Patent Appeals stated in In re Langer:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. Langer, 503 F.2d at 1391 (emphasis in original).

The "Langer" test for utility has been used in evaluation of rejections under 35 U.S.C. § 112, first paragraph, where the rejection is based on a deficiency under 35 U.S.C. § 101. An examiner cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description. Cortright, 165 F.3d at 1357. A reason to doubt an asserted utility may be established when the description "suggests an inherently unbelievable undertaking or involves implausible scientific principles." Brana, 51 F.3d at 1566.

In the present application, the Examiner rejects Claim 1 under 35 U.S.C. § 112, first paragraph, "since the claimed invention is not supported by either a clear asserted utility or well established utility for the reasons set forth [in the Examiner's rejection under 35 U.S.C. § 101] . . . one skilled in the art clearly would not know how to use the claimed invention." Applicants respectfully traverse the rejection as Applicants have established in the above remarks that the claimed invention has a specific and substantial credible utility.

A skilled artisan could easily follow the methodology for elucidating the presence of the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1), as disclosed in the patent application (and reiterated *supra*), on a non-differentiated patient population, in order to discern members of the population who manifest Alzheimer's disease.

Thus, one of skill in the art clearly would know how to use the claimed peptide (amino acid residues 2-14 of SEQ ID NO: 1) as a marker for Alzheimer's disease. Therefore, Applicants respectfully submit that the Examiner has failed to properly establish lack of enablement.

VIII. CONCLUSION

In conclusion, in light of the foregoing, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for lack of utility and lack of enablement in the present application. Favorable reconsideration of this application and withdrawal of the rejections of claim 1 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is courteously requested.

Respectfully submitted,

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IX. CLAIMS APPENDIX

Claim 1. An isolated biopolymer marker consisting of amino acid residues 2-14 of SEQ ID NO:1 which evidences a link to Alzheimer's disease.

X. EVIDENCE APPENDIX

A. Appellants rely on two declarations under 37 C.F.R. § 1.132.

1. The Declaration under 37 C.F.R. §1.132, filed on November 3, 2003, was entered into the prosecution record by the Examiner at page 6 of the Office Action mailed on May 28, 2004.

2. The Declaration under 37 C.F.R. § 1.132, filed on December 5, 2005, was entered into the prosecution record by the Examiner at page 5 of the Office Action mailed on February 28, 2006.

B. Appellants rely on four references, all previously presented to the Examiner in the Response filed on July 11, 2005.

1. Gunnersen et al. Proceedings of the National Academy of Science USA 89(24):11949-11953 1992

2. US 5,532,219 (McGeer et al.)

3. Cooper et al. Immunology Research 21(2-3):159-165 2000

4. Emmerling et al. Biochim Biophys Acta 1502(1):158-171 2000

Copies of the above-referenced declarations and references are attached hereto as forms the Evidence Appendix.

XI. RELATED PROCEEDINGS APPENDIX

NONE.

There have been no decisions rendered by a court or the Board in the related proceeding identified at Section II, page 5 of this paper.

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT	: Jackowski *et al.*
INVENTION	: Complement C3 Precursor Biopolymer Markers Indicative of Alzheimers Disease
SERIAL NUMBER	: 09/994,909
FILING DATE	: November 23, 2001
EXAMINER	: Chernyshev, Olga N.
GROUP ART UNIT	: 1646
OUR FILE NO.	: 2132.090

CERTIFICATE UNDER 37 CFR 1.8(a)
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DECLARATION UNDER 37 CFR § 1.132

I, Dr. George Jackowski, do hereby declare as follows:

1. I am Chief Executive Officer and Chief Science Officer of Syn-x Pharma Inc., assignee in the application entitled "**Complement C3 Precursor Biopolymer Markers Indicative of Alzheimers Disease**", having U.S. Application Serial No. 09/994,909 filed November 23, 2001.

2. In the Office Action mailed on July 29, 2003, claims 1 and 2 (as originally presented) were rejected under 35 U.S.C. 112, first paragraph because the claimed invention allegedly contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the invention is drawn to a biopolymer marker of SEQ ID NO:1 useful for indicating at least one particular disease state, for example, Alzheimers disease. The Examiner asserts that the experiments disclosed in the specification do not sufficiently support that the claimed peptide is a biopolymer marker of Alzheimers disease. The Examiner is particularly concerned with an alleged lack of controls in the experiments.

3. This declaration is submitted in order to clarify the use of controls in the experiments disclosed in the specification.

4. There are no conventional controls applied in the methods of the instant invention. Both samples from diseased patients and samples from healthy patients are separated by polyacrylamide gel electrophoresis. The gel is then examined in order to identify differences in the bands appearing in diseased and healthy patients. The bands, which differ between healthy and diseased patients, are excised and purified from the gel. A determination of up-regulation, down-regulation, presence and/or absence of the proteins present in the bands is assessed by sample wherein they appear, for example, the claimed peptide fragment was identified and excised from a band which appeared to be weakly expressed in the diseased samples as compared to the age-matched samples, thus this can be considered to be down-regulation of the protein in the

disease samples as compared to the increased presence of the protein in the age-matched samples. This comparison between two physiological states as evidenced by the bands appearing on the gel represents an inherent control in the experiment. The claimed protein fragment excised from the gel was sequenced and identified through the application of mass spectrometric techniques. It is standard laboratory practice to sequence peptides by mass spectrometry and identify the peptides based upon known sequences available in databases; without sequencing and comparing control peptides. One of ordinary skill in the art would be familiar with these standard protocols of mass spectrometry.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

Oct 29 2003
Date

George Jackowski

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICANT	: Jackowski *et al.*
INVENTION	: **Complement C3 Precursor Biopolymer Markers Indicative of Alzheimer's Disease**
SERIAL NUMBER	: 09/994,909
FILING DATE	: November 23, 2001
EXAMINER	: Chernyshev, Olga N.
GROUP ART UNIT	: 1649
OUR FILE NO.	: 2132.090

CERTIFICATE UNDER 37 CFR 1.8(a)
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Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR § 1.132

I, Ferris H. Lander, do hereby declare as follows:

1. I am a registered Patent Agent and am authorized to represent the inventor's and assignee in the application entitled **"Complement C3 Precursor Biopolymer Markers Indicative of Alzheimer's Disease"**, having U.S. Application Serial No. 09/994,909, filed November 23, 2001.

2. In the Final Office Action mailed on August 30, 2005, claim 1 (as presented on May 4, 2005) was rejected under 35 USC 101 because the claimed invention allegedly is drawn to an invention

with no apparent or disclosed specific and substantial credible utility. Claim 1 was also rejected under 35 U.S.C. 112, first paragraph because since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Specifically, the Examiner asserts that the instant specification fails to provide any evidence of record or rely on any prior art disclosure to support the assertion that the instant claimed fragment (amino acid residues 2-14 of SEQ ID NO:1) is useful for diagnosis or treatment of Alzheimer's disease.

3. Applicants submit that Figures 1 and 2, as originally filed, are "evidence of record" which supports Applicants' assertion of the usefulness of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) for diagnosis and/or treatment of Alzheimer's disease. Figure 2 shows a mass spectral profile obtained from Band 1 of the gel shown in Figure 1. Figure 2 also lists the ions identified from Band 1, including the claimed SEQ ID NO:1; an ion of complement C3 precursor protein weighing about 1682 daltons. Expression of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) was shown, in Figure 1, to be decreased in Alzheimer's disease patients versus age-matched control patients, and thus, the claimed peptide is differentially expressed in Alzheimer's disease versus age-matched controls.

4. In order to further illustrate this point, Applicants provide the attached figure entitled "DEAE 3(Elution) AD vs. Age

Matched AD (Control)" which represents Figure 1 as originally filed. The attached figure was produced by scanning the original photograph of the gel. Increased expression of Band C1(lanes 5-8, especially lane 5, all samples obtained from patients age-matched to the Alzheimer's disease patients) versus Band C2(lanes 1-4, especially lane 1, all samples obtained from Alzheimer's disease patients) is evident in the figure. Thus, decreased expression of the claimed peptide in Alzheimer's disease is also clearly shown. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any patent issuing thereon.

11/30/2005
Date

Ferris H. Lander
Ferris H. Lander
Reg. No. 43,377

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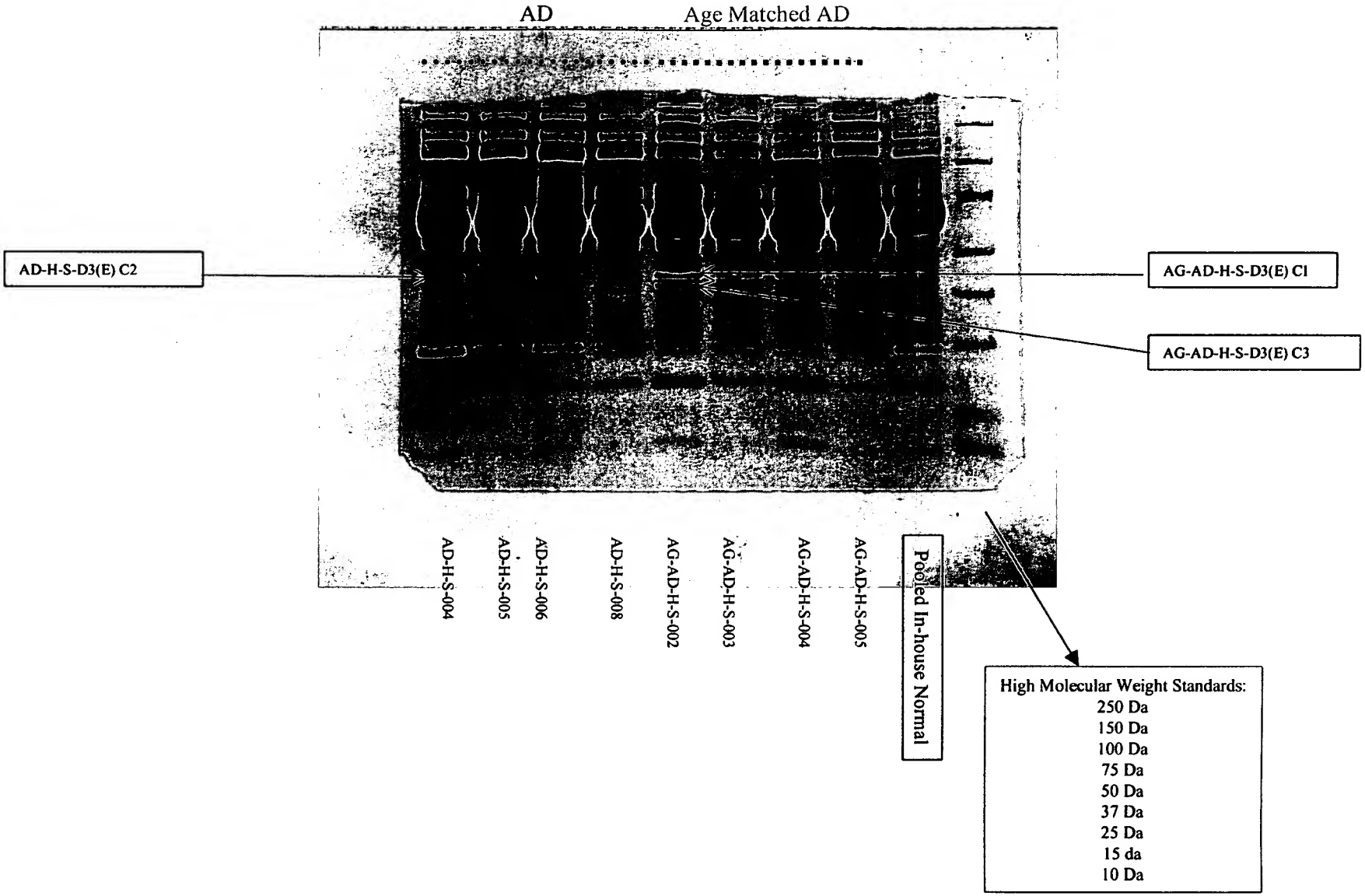
DEAE 3(Elution) AD vs. Age Matched AD (Control)



1: Proc Natl Acad Sci U S A. 1992 Dec 15;89(24):11949-53.

Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker.

Gunnersen D, Haley B.

Department of Biochemistry, College of Pharmacy, University of Kentucky, Lexington 40536-0084.

In this report, 8- and 2-azidoadenosine 5'-[gamma-32P] triphosphate were used to examine cerebrospinal fluid (CSF) samples for the presence of an ATP binding protein unique to individuals with Alzheimer disease (AD). A 42-kDa ATP binding protein was found in the CSF of AD patients that is not observed in CSF from normal patients or other neurological controls. The photolabeling is saturated with 30 microM 2-azidoadenosine 5'-[gamma-32P]triphosphate. Photoinsertion can be totally prevented by the addition of 25 microM ATP. Photoinsertion of 2-azidoadenosine 5'-triphosphate into the protein is only weakly protected by other nucleotides such as ADP and GTP, indicating that this is a specific ATP binding protein. A total of 83 CSF samples were examined in a blind manner. The 42-kDa protein was detected in 38 of 39 AD CSF samples and in only 1 of 44 control samples. This protein was identified as glutamine synthetase [GS; glutamate-ammonia ligase; L-glutamate:ammonia ligase (ADP-forming), EC 6.3.1.2] based on similar nucleotide binding properties, comigration on two-dimensional gels, reaction with a polyclonal anti-GS antibody, and the presence of significant GS enzyme activity in AD CSF. In brain, GS plays a key role in elimination of free ammonia and also converts the neurotransmitter and excitotoxic amino acid glutamate to glutamine, which is not neurotoxic. The involvement of GS, if any, in the onset of AD is unknown. However, the presence of GS in the CSF of terminal AD patients suggests that this enzyme may be a useful diagnostic marker and that further study is warranted to determine any possible role for glutamate metabolism in the pathology of AD.

PMID: 1361232 [PubMed - indexed for MEDLINE]

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Dec 18 2006 06:34:27

1: Immunol Res. 2000;21(2-3):159-65.

Focal inflammation in the brain: role in Alzheimer's disease.

Cooper NR, Bradt BM, O'Barr S, Yu JX.

Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA. nrcooper@scripps.edu

We hypothesize that amyloid (Abeta) peptide-containing neuritic plaques in the brains of patients with Alzheimer's disease represent chronic inflammatory foci mediated by the actions of the complement system and proinflammatory cytokines. In support of this, in vitro studies show that the (Abeta) peptide is a potent complement activator and that such complement activation leads to the formation of covalent (Abeta)-C3 activation fragment complexes, the generation of the chemokine-like C5a complement activation peptide, and the formation of the proinflammatory C5b-9 complex in functionally active form able to insert into neuronal cell membranes. Other studies show that C5a, together with (Abeta), synergistically augments the release of proinflammatory cytokines from human monocytes. These studies, which provide in vitro support for the hypothesis, are being pursued in an animal model of Alzheimer's disease.

PMID: 10852113 [PubMed - indexed for MEDLINE]

1: Biochim Biophys Acta. 2000 Jul 26;1502(1):158-71.

ELSEVIER FULL-TEXT ARTICLE Links

The role of complement in Alzheimer's disease pathology.

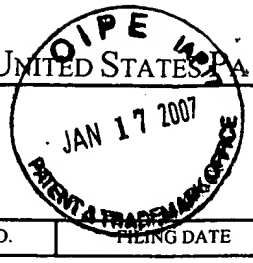
Emmerling MR, Watson MD, Raby CA, Spiegel K.

Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, MI 48106, USA.
mark.emmerling@wl.com

Complement proteins are integral components of amyloid plaques and cerebral vascular amyloid in Alzheimer brains. They can be found at the earliest stages of amyloid deposition and their activation coincides with the clinical expression of Alzheimer's dementia. This review will examine the origins of complement in the brain and the role of beta-amyloid peptide (Abeta) in complement activation in Alzheimer's disease, an event that might serve as a nidus of chronic inflammation. Pharmacology therapies that may serve to inhibit Abeta-mediated complement activation will also be discussed.

PMID: 10899441 [PubMed - indexed for MEDLINE]

01-18-07



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/994,909	11/23/2001	George Jackowski	2132.090	7376

21917 7590 12/14/2006

MCHALE & SLAVIN, P.A.
2855 PGA BLVD
PALM BEACH GARDENS, FL 33410

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No. 09/994,909	Applicant(s) JACKOWSKI ET AL.	
	Examiner Olga Chernyshev	Art Unit 1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *13 November 2006* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file anamended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☐ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☐ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☐ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☐ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner **and relied upon by appellant in the appeal**, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☐ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☐ Other (including any explanation in support of the above items):

(1) Appeal Briefs are no longer filed under C.F.R 1.192 ,but C.F.R. 41.37
SECTION IX ,X: Brief does not contain the headings (ix) Evidence Appendix and (x) Related Proceedings Appendix. These sections must have a separate heading within the brief with a note of "None" if there are no Related Proceedings or Evidence present. Signature block and signature of attorney of record or authorizing offical is missing .

/ Everett R. Williams/
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Patent Appeals Specialist

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